[0011] Particularly preferred procytotoxins have the following structures: (1) Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-[Gln-Gly-Ala-Ile-Gly-Gln-Pro]-(X) (SEQ ID NOS 1 & 2, respectively), and (2) Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-[Gln- Ser-Ser-Phe(or Tyr)-Tyr-Ser-Gly(or Ser)]-(X) (SEQ ID NOS 3 & 4, respectively), wherein (X) is the inactivator as described herein and the peptide marked in brackets can be oriented in either direction. The inactivator, for example, can be a microbead, amino acid, peptide, phage, or phage filament. Preferably, the procytotoxin further contains a targeting molecule. Still preferred, the targeting molecule is a neovascular targeting sequence of an anti-fibronectin ED-B antibody. Also preferred, the targeting molecule is an RGD targeting sequence.

Please delete paragraph [0012], and replace it with the following paragraph:

[0012] Other preferred procytotoxins further are charge neutralized, in addition to steric determinants. For example, Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys(R)-Arg-Lys(R)-Arg-Gln-[Gln-Gly-Ala-Ile-Gly-Gln-Pro]-(X) (SEQ ID NOS 21 & 22, respectively), wherein (X) is the inactivator as described herein, the peptide marked in brackets can be oriented in either direction, and wherein R is independently selected from the group consisting of the [unmodified ε-amino group of the adjacent lysine residue], [ε-γ]-Glu, [ε-γ]-Glu-[α-γ]-$(Glu)_{1-3}$, [ε-α]-$(Phe)_{1-3}$, [ε-α]-$(Tyr)_{1-3}$, [ε-α]-$(Trp)_{1-3}$, [ε-α]-$(Lys)_{1-3}$ and [ε-α]-$(Arg)_{1-3}$, wherein [ε-γ] represents a peptide bond between the epsilon amino group of lysine and the gamma carboxyl group of the adjacent glutamate, [α-γ] represents a peptide bond between the alpha amino group of the first glutamate and the gamma carboxyl group of the second glutamate, [ε-α] represents a peptide bond between the epsilon amino acid of lysine and the alpha carboxyl group of the indicated amino acid and the subscript indicates that additional numbers of the designated amino acid can be linked to the first via conventional peptide bonds.

Please delete Table 1 on page 8, and replace it with the following Table:

TABLE 1 Amin Acid Sequ nce f Selected Cyt lytic Peptides

Amoebapore Helix 3 (*Entamoeba histolytica*)

NH_2-Gly-Phe-Ile-Ala-Thr-Leu-Cys-Thr-Lys-Val-Leu-Asp-Phe-Gly-Ile-Asp-Lys-Leu-Ile-Gln-Leu-Ile-Glu-Asp-Lys-$CONH_2$ (SEQ ID NO: 5)

Cecropin A (*Antheria pernyi*)

NH_2-Lys-Trp-Lys-Leu-Phe-Lys-Lys-Ile-Glu-Lys-Val-Gly-Gln-Asn-Ile-Arg-Asp-Gly-Ile-Ile-Lys-Ala-Gly- Pro-Ala-Val-Ala-Val-Val-Gly-Gln-Ala-Thr-Gln-Ile-Ala-Lys-COOH (SEQ ID NO: 6)

Cecropin B (*Antheria pernyi*)

NH_2-Lys-Trp-Lys-Ile-Phe-Lys-Lys-Ile-Glu-Lys-Val-Gly-Arg-Asn-Ile-Arg-Asn-Gly-Ile-Ile-Lys-Ala-Gly-Pro-Ala-Val-Ala-Val-Leu-Gly-Glu-Ala-Lys-Ala-Leu-COOH (SEQ ID NO: 7)

Cecropin D (*Antheria pernyi*)

NH_2-Trp-Asn-Pro-Phe-Lys-Glu-Leu-Glu-Lys-Val-Gly-Gln-Arg-Val-Arg-Asp-Ala-Val-Ile-Ser-Ala-Gly-Pro-Ala-Val-Ala-Thr-Val-Ala-Gln-Ala-Thr-Ala-Leu-Ala-Lys-COOH (SEQ ID NO: 8)

Melittin (*Apis mellifera*)

NH_2-Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-Gln-COOH (SEQ ID NO: 9)

Please delete paragraph [0025], and replace it with the following paragraph:

[0025] Three isoforms of amoebapore are known: amoebapore A, B and C, respectively. This peptide is stabilized by three disulfide bonds and contains four mostly amphipathic alpha-helical structures. The third amphipathic helical structure (helix 3) retains the cytolytic activity similar to the wild type peptide. A synthetic peptide based on the sequence of its third amphipathic alpha helix have recently been

shown to have cytolytic activity for nucleated cells at high concentrations (10-100 μM) (Leippe *et al.*, (1994) Proc. Natl. Acad. Sci. USA 91: 2602). Accordingly, a particularly preferred cytotoxin is a derivative of the amoebapore cytolytic peptide listed in Table I: NH_2-Gly-Phe-Ile-Ala-Thr-Leu-Cys-Thr-Lys-Val-Leu-Asp-Phe-Gly-Ile-Asp-Lys-Leu-Ile-Gln-Leu-Ile-Glu-Asp-Lys-$CONH_2$ (SEQ ID NO: 5).

Please delete paragraph [0053], and replace it with the following paragraph:

[0053] For instance, the procytotoxin of the present invention comprises the following structure: Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-[Gln-Gly-Ala-Ile-Gly-Gln-Pro]-(X) (SEQ ID NOS 1 & 2, respectively), wherein (X) is an inactivator and the peptide marked in brackets can be oriented in either direction. The inactivator can be selected from the group consisting of a microbead, an amino acid, a peptide, phage and a phage filament. Cleavage by MMP at this peptide will yield a melittin peptide with few additional amino acids on the C-terminus (Gly-Ala-Ile) which should not interfere with pore formation.

Please delete paragraph [0054], and replace it with the following paragraph:

[0054] In a related vein, the procytotoxin of the present invention comprises Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-[Gln- Ser-Ser-Phe(or Tyr)-Tyr-Ser-Gly(or Ser)]-(X) (SEQ ID NOS 3 & 4, respectively), wherein (X) is an inactivator and the peptide marked in brackets can be oriented in either direction. Cleavage of this peptide with PSA will render the peptide toxic.

Please delete paragraph [0055], and replace it with the following paragraph:

[0055] Also contemplated in the instant invention is a targeting molecule that adds an additional measure of selectivity. For example, the procytotoxin may comprise the following structure: lytic peptide-[Gln-Gly-Ala-Ile-Gly-Gln-Pro]-Lys-[ε-γ]-biotin- (SEQ ID NO: 10) streptavidin coated microbead-RGD targeting sequence.

Please delete paragraph [0060], and replace it with the following paragraph:

[0060] Particularly preferred procytotoxins include amoebapore, its analogs and its derivatives that contains one or more γ-linked glutamate residues linked via a peptide bond to the epsilon amino group of at least one lysine, preferably the C-terminal-most lysine (hereinafter "γ-glutamate-masked amoebapore analog"). A particularly preferred procytotoxin has the following structure: Gly-Phe-Ile-Ala-Thr-Leu-Cys-Thr-Lys-Val-Leu-Asp-Phe-Gly-Ile-Asp-Lys-Leu-Ile-Gln-Leu-Ile-Glu-Asp-Lys-[ε-γ]-Glu-[α-γ]-Glu (SEQ ID NO: 11), wherein [ε-γ] represents a peptide bond between the epsilon amino group of lysine and the gamma carboxyl group of the adjacent glutamate and [α-γ] represents a peptide bond between the alpha amino group of the first glutamate and the gamma carboxyl group of the second glutamate.

Please delete paragraph [0061], and replace it with the following paragraph:

[0061] In addition, amoebapore and other cytotoxic peptides can be modified with other amino acids. One such exemplary protoxin has the following structure: Gly-Phe-Ile-Ala-Thr-Leu-Cys-Thr-Lys-Val-Leu-Asp-Phe-Gly-Ile-Asp-Lys-Leu-Ile-Gln-Leu-Ile-Glu-Asp-Lys-[ε-α]-Phe (SEQ ID NO: 12), wherein [ε-α] represents a peptide bond between the epsilon amino group of lysine and the alpha carboxyl group of the adjacent phenylalanine. Another exemplary protoxin that can be activated by chymotrypsin-like activity has the following structure: Gly-Phe-Ile-Ala-Thr-Leu-Cys-Thr-Lys-Val-Leu-Asp-Phe-Gly-Ile-Asp-Lys([ε-α]-Phe)-Leu-Ile-Gln-Leu-Ile-Glu-Asp-Lys-[ε-α]-Phe (SEQ ID NO: 13), using the same nomenclature and where Lys([ε-α]-Phe)-Leu represents a linkage between the epsilon amino group of lysine and the alpha carboxy group of phenylalanine, and a standard peptide linkage between lysine and phenlyalanine. Of course, the phenylalanine may be replaced with other amino acids, such as tyrosine and tryptophan in the case of chymotrypsin-like activity. In some instances, in order to invoke trypsin-like activity, it may be beneficial to utilize positively charged amino acids, like arginine and lysine, instead of phenylalanine.

Please delete paragraph [0062], and replace it with the following paragraph:

[0062] Other particularly preferred procytotoxins include melittin, its analogs and its derivatives that contain at least one γ-linked glutamate residue linked via a peptide bond to the epsilon amino group of a lysine (hereinafter "γ-glutamate-masked

melittin analog"). As indicated in Table 1, melittin has two lysines and two adjacent arginines near its C-terminus. When one of the lysines is so masked, it is expected that the free alpha carboxyl group would act to neutralize the adjacent arginine, further contributing to the inhibition of the toxic activity of melittin. A particularly preferred procytotoxin has the following structure: Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys([ε-γ]-Glu)-Arg-Lys([ε-γ]-Glu)-Arg-Gln-Gln (SEQ ID NO: 14), wherein -Lys-([ε-γ]-Glu)-Arg- represents a peptide bond between the epsilon amino group of lysine and the gamma carboxyl group of the adjacent glutamate and a standard peptide bond between the lysine and arginine residues. Of course, -Lys-([ε-γ]-Glu)-Arg- can be replaced, for example, by -Lys([ε-α]-Phe)-Leu-, as detailed above, and phenylalanine can be replaced by other amino acids like tyrosine and tryptophan to invoke chymotrypsin-like activity. In some instances, when trypsin-like activity is being invoked, it may be beneficial to utilize positively charged amino acids, like arginine and lysine, instead of phenylalanine in this latter example.

Please delete paragraph [0064], and replace it with the following paragraph:

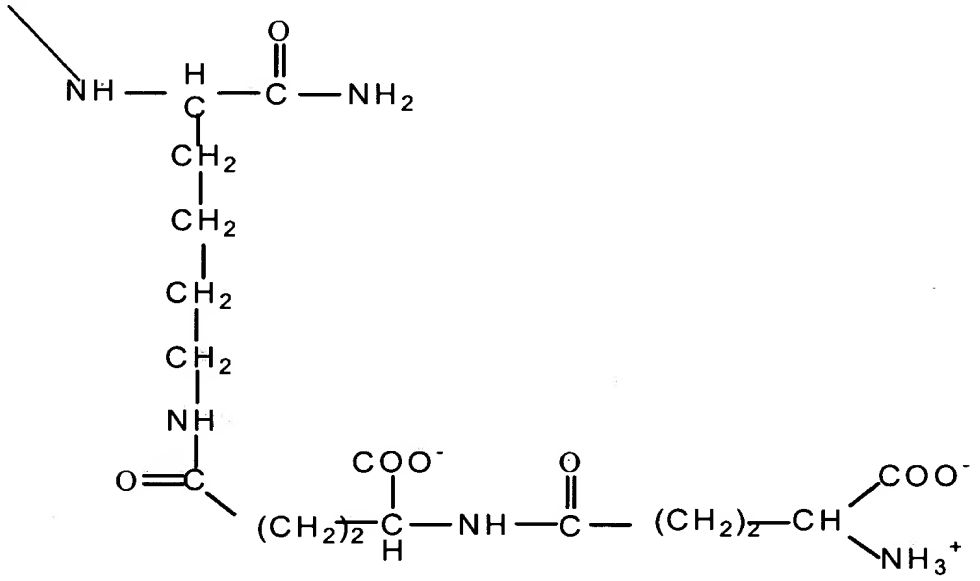
[0064] A set of particularly preferred procytotoxins have the following structures: (1) Gly-Phe-Ile-Ala-Thr-Leu-Cys-Thr-Lys(R)-Val-Leu-Asp-Phe-Gly-Ile-Asp-Lys(R)-Leu-Ile-Gln-Leu-Ile-Glu-Asp-Lys(R) (SEQ ID NO: 15), and (2) Gly- Ile-Gly-Ala-Val-Leu-Lys(R)-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys(R)-Arg-Lys(R)-Arg-Gln-Gln (SEQ ID NO: 16), wherein R is independently selected from the group consisting of the ε-amino group of the adjacent lysine residue, [ε-γ]-Glu, [ε-γ]-Glu-[α-γ]-$(Glu)_{1-3}$, [ε-α]-$(Phe)_{1-3}$, [ε-α]-$(Tyr)_{1-3}$, [ε-α]-$(Trp)_{1-3}$, [ε-α]-$(Lys)_{1-3}$ and [ε-α]-$(Arg)_{1-3}$, wherein [ε-γ] represents a peptide bond between the epsilon amino group of lysine and the gamma carboxyl group of the adjacent glutamate, [α-γ] represents a peptide bond between the alpha amino group of the first glutamate and the gamma carboxyl group of the second glutamate, [ε-α] represents a peptide bond between the epsilon amino acid of lysine and the alpha carboxyl group of the indicated amino acid and the subscript indicates that additional numbers of the designated amino acid can be linked to the first via conventional peptide bonds. With regard to the subscripted numbers, it is understood that larger numbers of amino acids are possible, *e.g.*, 4, 5, 6, *etc.*, but 1, 2, and 3 are anticipated to be optimal.

Please delete paragraph [0092], and replace it with the following paragraph:

[0092] Below is shown a diagram of the initial cytolytic peptide and the procytolytic peptide synthesized by the addition of the two γ glutamate linked side-chain glutamic acid residue to the ε amino group of the C-terminal lysine.

Cytolytic Peptide: (SEQ ID NO: 17)
N-Gly-Phe-Ile-Ala-Thr-Leu-Cys-Thr-Lys-Val-Leu-Asp-Phe-Gly-Ile-Asp-Lys-Leu-Ile-Gln-Leu-Ile-Glu-Asp-Lys-$CONH_2$

Procytolytic Peptide: (SEQ ID NO: 18)
N-Gly-Phe-Ile-Ala-Thr-Leu-Cys-Thr-Lys-Val-Leu-Asp-Phe-Gly-Ile-Asp-Lys-Leu-Ile-Gln-Leu-Ile-Glu-Asp—



Please delete paragraph [0097], and replace it with the following paragraph:

[0097] This example demonstrates that the inventive γ-glutamate-masked cytolytic peptides have specificity for cancer cells other than those expressing PSMA. This experiment, utilized a melittin analog having A [ε-γ]-Glu-[α-γ]-Glu at each of lysines 21 and 23: NH_2-Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys([ε-γ]-Glu-[α-γ]-Glu)-Arg-Lys([ε-γ]-Glu-[α-γ]-Glu)-Arg-Gln-Gln-COOH (SEQ